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03 EP	03745226.5	PCT		
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04	001 Filing fee - EP direct	EUR	_	
05	002 Search fee	EUR		
06	005 Designation fee(s) <sup>1</sup>	EUR		
07	015 Claims fee(s) (Rules 45(1), 162(1) EPC)	EUR	_	
08	055 Additional copy	EUR		
09	006 Examination fee	EUR	_	
10	007 Fee for grant including fee for printing (up to 35 pages)	EUR		
11	O08 Additional fee for printing (more than 35 pages)	EUR	_	
12	033 Renewal fee for the 3rd year	EUR		
13	034 Renewal fee for the 4th year	EUR		
14	035 Renewal fee for the 5th year	EUR	_	
15	020 Filling fee – entry EP phase	EUR		
16	Extension fee(s) for *:	EUR	_	
17	Fee for further processing	EUR 210.00		
18		EUR		
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22	7	Total EUR 210.00		
Signature	Nonno Sellino	London, 12 September 2008		

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## THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

- 1. A method of modulating sphingosine kinase functional activity in vitro, said method comprising contacting said sphingosine kinase with an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of said sphingosine kinase wherein said agent agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or acts as a phosphorylation catalyst of sphingosine kinase.
- 2. A method of modulating cellular activity in vitro, said method comprising contacting said cell with an effective amount of an agent for a time and under conditions sufficient to modulate the phosphorylation of sphingosine kinase wherein said agent agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or acts as a phosphorylation catalyst of sphingosine kinase.
- 3. The method according to claim 1 or 2 wherein said sphingosine kinase is human sphingosine kinase.
- 4. The method according to any one of claims 1-3 wherein said phosphorylation is modulated at  $S^{225}$ .
- The method according to claim 4 wherein said agent binds, links or otherwise associates with S<sup>225</sup>.
- 6. The method according to any one of claims 1-5 wherein modulation of said phosphorylation is modulation of proline-directed protein kinase catalysed phosphorylation.
- 7. The method according to claim 6 wherein said proline directed kinase is ERK1, ERK2 or CDK2.

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- 8. The method according to claim 7 wherein said proline directed kinase is ERK2.
- The method according to any one of claims 1-8 wherein said modulation is downregulation.
- 10. An agent which antagonises the interaction between sphingosine kinase and a phosphorylation catalyst for use in the apeutically downregulating inflammation or cellular proliferation.
- 11. An agent which agonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst for use in therapeutically stimulating cellular proliferation or inflammation.
- 12. The agent according to claim 10, wherein said agent is for use in the treatment of a condition which is characterised by inflammation or unwanted cellular proliferation in a mammal.
- 13. The agent according to any one of claims 10 to 12 wherein said sphingosine kinase is human sphingosine kinase.
- 14. The agent according to any one of claims 10-13 wherein said phosphorylation is modulated at S<sup>225</sup>.
- 15. The agent according to claim 14 wherein said agent binds, links or otherwise associates with S<sup>225</sup>.
- 16. The agent according to any one of claims 10-15 wherein said phosphorylation catalyst is a proline-directed protein kinase.
- 17. The agent according to claim 16 wherein said proline directed protein kinase is ERK1, ERK2 or CDK2.

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- 18. The agent according to claim 17 wherein said proline directed kinase is ERK2.
- 19. The agent according to claims 10-11 or 12-18 wherein said inflammation is induced by TNF.
- 20. The agent according to claim 10 or 12-18 wherein said cellular proliferation is neoplastic proliferation, TNF-induced cellular proliferation and/or anti-apoptotic activity.
- 21. The agent according to claim 10 or 12-18 wherein said inflammation is inflammatory mediator production and/or adhesion molecule expression.
- 22. The agent according to claim 10 or 12-18 wherein said inflammation is associated with rheumatoid arthritis, atherosclerosis, asthma, autoimmune disease or inflammatory bowel disease.
- 23. Use of an agent in the manufacture of a medicament for the treatment of a condition in a mammal, which condition is characterised by inflammation or unwanted cellular proliferation, wherein said agent antagonises the interaction between sphingosine kinase and a phosphorylation catalyst.
- 24. Use according to claim 23 wherein said sphingosine kinase is human sphingosine kinase.
- 25. Use according to any one of claims 23-24 wherein said phosphorylation is modulated at S<sup>225</sup>.
- 26. Use according to claim 25 wherein said agent binds, links or otherwise associates with S<sup>225</sup>.
- 27. Use according to any one of claims 23-26 wherein said phosphorylation catalyst is

(ADocuments and Semagn) MakeglewaterLocal Scalings/Temporary Internet File/QLE.11/FBO claims 12.9 2008 class (Z).46c-12/09/2008,

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a proline-directed protein kinase.

- 28. Use according to claim 27 wherein said proline directed kinase is ERK1, ERK2 or CDK2.
- Use according to claim 28 wherein said proline directed kinase is ERK2.
- 30. Use according to claim 23-29 wherein said inflammation is induced by TNF.
- 31. Use according to claim 23-29 wherein said condition is a neoplastic condition.
- 32. Use according to claim 23-30 wherein said inflammation is inflammatory mediator production and/or adhesion molecular expression.
- 33. Use according to claim 23-30 or 32 wherein said inflammatory condition is rheumatoid arthritis, atherosclerosis, asthma, autoimmune disease or inflammatory bowel disease.
- 34. An isolated sphingosine kinase variant comprising a mutation at one or more of S<sup>148</sup>, S<sup>181</sup>, Y<sup>184</sup>, S<sup>225</sup> or T<sup>250</sup>, wherein said variant exhibits ablated or reduced phosphorylation capacity relative to wild-type sphingosine kinase or a functional derivative, homologue or analogue thereof.
- 35. An isolated sphingosine kinase variant comprising a mutation at one or more of S<sup>148</sup>, S<sup>181</sup>, Y<sup>184</sup>, S<sup>225</sup> or T<sup>250</sup>, wherein said variant exhibits enhanced or up-regulated phosphorylation capacity relative to wild-type sphingosine kinase or a functional derivative, homologue or analogue thereof.
- 36. The isolated variant of claim 34 wherein said variant comprises an amino acid sequence with a single or multiple amino acid substitution and/or deletion of amino acid S<sup>225</sup>.

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The isolated variant of claim 36 wherein said substitution is a Ser<sup>225</sup> Ala 37. substitution.

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## THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of modulating sphingosine kinase functional activity in vitro, said method comprising contacting said sphingosine kinase with an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of said sphingosine kinase wherein said agent agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or acts as a phosphorylation catalyst of sphingosine kinase.

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2. A method of modulating cellular activity in vitro, said method comprising contacting said cell with an effective amount of an agent for a time and under conditions sufficient to modulate the phosphorylation of sphingosine kinase wherein said agent agonises or antagonises the interaction between sphingosine kinase and a phosphorylation catalyst or acts as a phosphorylation catalyst of sphingosine kinase.

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- The method according to claim 1 or 2 wherein said sphingosine kinase is human sphingosine kinase.
- The method according to any one of claims 1-3 wherein said phosphorylation is modulated at S<sup>225</sup>.
- 5. The method according to claim 4 wherein said agent binds, links or otherwise associates with S<sup>225</sup>.
- 6. The method according to any one of claims 1-5 wherein modulation of said phosphorylation is modulation of proline-directed protein kinase catalysed phosphorylation.
- 7. The method according to claim 6 wherein said proline directed kinase is ERK1, ERK2 or CDK2.

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The method according to claim 7 wherein said proline directed kinase is ERK2.

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- The method according to any one of claims 1-8 wherein said modulation is down-9. regulation.
- An agent which antagonises the interaction between sphingosine kinase and a phosphorylation catalyst for use in therapeutically downregulating inflammation or cellular proliferation.
- An agent which agonises the interaction between sphingosine kinase and a phosphorylation catalyst or which acts as a phosphorylation catalyst of sphingosine kinase for use in therapeutically stimulating cellular proliferation or inflammation.
- The agent according to claim 10, wherein said agent is for use in the treatment of a condition which is characterised by inflammation or unwanted cellular proliferation in a mammal.
- 13. The agent according to any one of claims 10 to 12 wherein said sphingosine kinase is human sphingosine kinase.
- 14. The arent according to any one of claims 10-13 wherein said phosphorylation is modulated at S<sup>225</sup>.
- 15. The agent according to claim 14 wherein said agent binds, links or otherwise associates with S<sup>225</sup>.
- 16. The agent according to any one of claims 10-15 wherein said phosphorylation catalyst is a proline-directed protein kinase.
- 17. The agent according to claim 16 wherein said proline directed protein kinase is ERK1, ERK2 or CDK2.

Deleted: 10. The method according to claim 9 wherein said agent is U0126. ¶

11. The method according to claim 9 wherein said agent is PD98059. ¶

A method for the treatment and/or prophylaxis of a condition in a mammal, which condition is in a mammal, which constant is characterised by shortant, unwanted or otherwise inappropriate cellular activity, sald method comprising administering to said mammal an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates sald cellular activity and inhibiting or otherwise antagonising said 

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19. The agent according to claims 10-11 or 12-18 wherein said inflammation is	Deleted: 20. The metho [4]
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22 The agent according to claim 10 or 12-18 wherein said inflammation is associated	pelebed: motod
22. The agent according to claim 10 of 12-16 wherein said minimum as 22.	Deleted:
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23. Use of an agent in the manufacture of a medicament for the treatment of a	Delebad: method
condition in a mammal, which condition is characterised by inflammation or unwanted	Deleted: 23 or 24
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cellular proliferation, wherein said agent antagonises the interaction between sphingosine	Deleted: 26. The method [8]
kinase and a phosphorylation catalyst.	Deleted: aberrant, Deleted: or otherwise [ [9]]
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25. Use according to any one of claims 23-24 wherein said phosphorylation is	Deleted: 28-30
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25 wherein and agent hinds links or otherwise associates	Deleted: 32
26. Use according to claim 25 wherein said agent binds, links or otherwise associates	Deleted: 31
with S <sup>225</sup> .	
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27. Use according to any one of claims 23-26 wherein said phosphorylation catalyst is	Deleted: modulation of

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١,٠	28. Use according to claim 27 wherein said proline directed kinase is ERK1, ERK2 or	Deleted: 33
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	29. Use according to claim 28 wherein said proline directed kinase is ERK2.	Deleted: 34
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i	30. Use according to claim 23-29 wherein said inflammation is induced by TNF.	any one of claims 28-35 wherein said modulation is down [12]
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٠	33. Use according to claim 23-30 or 32 wherein said inflammatory condition is	Deleted: 39 or 40
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	34. An isolated sphingosine kinase variant comprising a mutation at one or more of	Deleted: 1
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	35. An isolated sphingosine kinase variant comprising a mutation at one or more of	Formatted: Superscript
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	derivative, homologue or analogue thereof.	Formatted: Superscript
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	36. The isolated variant of claim 34 wherein said variant comprises an amino acid	
	36. The isolated variant of claim 24 was said a sold and deletion of amino acid	Formatted: Superscript
	sequence with a single or multiple amino acid substitution and/or deletion of amino acid	Deleted: 48
	S <sup>225</sup> .	Deleted: 46
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37. The isolated variant of claim 36 wherein said substitution is a Ser<sup>225</sup> Ala substitution.

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- The method according to claim 9 wherein said agent is PD98059.
- 12. A method for the treatment and/or prophylaxis of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate cellular activity, said method comprising administering to said mammal an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up- regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity.
- 13. A method for the treatment and/or prophylaxis of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate sphingosine kinase functional activity, said method comprising administering to said mammal an effective amount of an agent for a time and under conditions sufficient to modulate phosphorylation of sphingosine kinase wherein inducing or otherwise agonising said phosphorylation up-regulates said sphingosine kinase functional activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said sphingosine kinase functional activity.

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23. The method according to claim 21 wherein said condition is an inflammatory condition and said cellular activity is the production of inflammatory mediators.

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Page 61:[7] Deleted 4 13:48:00 inflammatory condition is

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11/09/2008 10:59:00 26. The method according to any one of claims 20-25 wherein said agent is U0126.

The method according to any one of claims 20-25 wherein said agent is 27. PD98059.

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Page 61: [9] Deleted 11:00:00 or otherwise inappropriate

Page-61: [40] Defected. 11:00:00 modulates the phosphorylation of sphingosine kinase and wherein inducing or otherwise agonising said phosphorylation up-regulates said cellular activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said cellular activity

Page 61: [11] Deleted 11:00:00 Use of an agent in the manufacture of a medicament for the treatment of a condition in a mammal, which condition is characterised by aberrant, unwanted or otherwise inappropriate sphingosine kinase activity, wherein said agent modulates the phosphorylation of sphingosine kinase and wherein inducing or otherwise agonising said phosphorylation up-regulates said sphingosine kinase activity and inhibiting or otherwise antagonising said phosphorylation down-regulates said sphingosine kinase activity.

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Use according to any one of claims 28-35 wherein said modulation is downregulation.

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and said cellular activity is TNF-induced cellular proliferation and/or anti-apoptotic characteristic

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Use according to claim 37 wherein said condition is an inflammatory condition and said cellular activity is the production of inflammatory mediators.

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Use according to any one of claims 36-41 wherein said agent is U0126.

- Use according to any one of claims 36-41 wherein said agent is PD98059. 43.
- A pharmaceutical composition comprising an agent, which agent modulates 44. phosphorylation of sphingosine kinase, together with one or more pharmaceutically acceptable carriers and/or diluents when used in accordance with the method of any one of claims 1-27.
- An agent, which agent modulates phosphorylation of sphingosine kinase, 45. when used in accordance with the method of any one of claims 1-27.

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Page 62: [18] Deleted: 11/09/2008 11:04:00 in a region of said sphingosine kinase which region comprising a phosphorylation site